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Quantitative Correlation between Molecular Similarity and Receptor-Binding Activity of Neonicotinoid Insecticides

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Abstract: Quantitative correlation between molecular similarity and receptor-binding activity of neonicotinoid insecticides such as imidacloprid and acetamiprid was studied by using a method of similarity index and semi-empirical molecular orbital calculations. A series of compounds having an aromatic ring and a cyclic or acyclic amine moiety with an electron-withdrawing group were subjected to the similarity-activity analysis. Energy-minimum structures and electrostatic properties of the molecules were obtained by MNDO-PM3. The electrostatic similarity of each molecule compared with the most active compounds was found to correlate significantly with the binding activity to nicotinic acetylcholine receptor (nAChR) in honey bee when the two molecules were superimposed to maximize the molecular shape similarity by simplex procedure. This indicates that molecular similarity in terms of electrostatic properties is important for activity, as well as superimposability in terms of molecular shape. A schematic model of interaction between neonicotinoids and nAChR is proposed according to the results of similarity-activity analyses. © 1998 SCI.

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Key words: neonicotinoid; similarity index; receptor-binding activity; nicotinic acetylcholine receptor; molecular orbital calculation; MNDO-PM3; molecular recognition

1 INTRODUCTION

A number of neonicotinoid insecticides have been discovered as agonists of the nicotinic acetylcholine receptor (nAChR).[1] We have recently developed acetamiprid[2,3] as one of the neonicotinoids, which has an *N*-cyanoacetamidine structure as its characteristic feature. In our previous study to predict the active conformation of acetamiprid,[4] we investigated the molecular similarity between acetamiprid and another neonicotinoid, imidacloprid,[5] which has an *N*-nitroguanidine structure. It was found that the molecular similarity indices in terms of steric and electrostatic properties were helpful to understand the bioisosterism of these two insecticides having different structural features. This result suggested that the method of similarity index may be useful as a quantitative measure of molecular similarity to account for the structure–activity profiles of neonicotinoid insecticides. Based on such a background, we have studied the correlation between molecular similarity and receptor-binding activity of a series of neonicotinoid insecticides. This paper describes the result of the correlation analysis, and a model of molecular recognition at the receptor will be presented based on the structure–activity analysis.

2 MATERIALS AND METHODS

2.1 Compounds and biological activity

Among a number of neonicotinoid insecticides, we have investigated the compounds having a general structure

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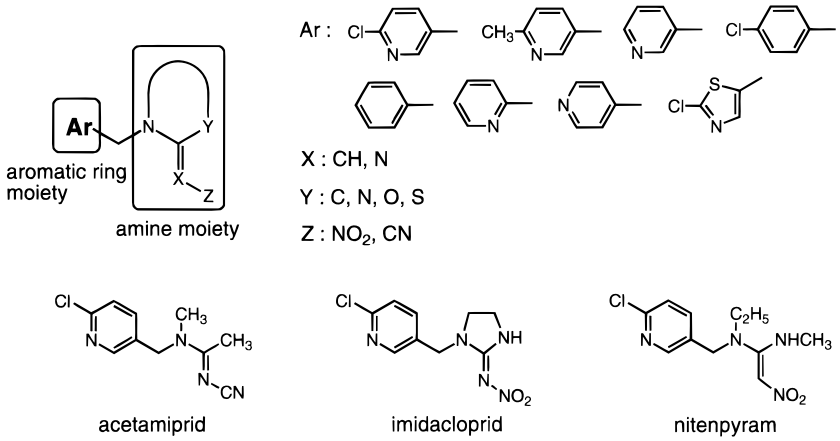


Fig. 1. Structures of neonicotinoid insecticides studied in this paper. Structural variation and the representatives of developed insecticides.

shown in Fig. 1, in which an amine moiety with an electron-withdrawing group and an aromatic ring moiety are jointed by a methylene, since most of the well-known neonicotinoids such as imidacloprid,[5] acetamiprid[2,3] and nitenpyram[6] have this structural feature, and many analogous compounds have been reported. The receptor-binding activities (K_i) of neonicotinoids having various structures in both structural moieties were reported by Tomizawa and Yamamoto.[1] We have employed the K_i values against nAChR of honey bee from their paper, and the pK_i ($= -\log K_i$; K_i is in M) was used as the index of biological activity for the receptor binding.

2.2 Molecular orbital calculation

Structures of neonicotinoids and their model molecules were optimized by semi-empirical molecular orbital calculations using MNDO-PM3[7,8] with MOPAC program.[9] Initial structures of the molecules were constructed by considering the crystal structure of imidacloprid[10] and the result of conformational analysis of acetamiprid.[4] Then the energy-minimum structure of each molecule was obtained by geometry optimization. The molecular electrostatic potentials of the molecules were computed from the ESP atomic charges derived from electrostatic potentials[11] by using the ESP option in MOPAC.

2.3 Molecular similarity indices

As quantitative measures of molecular similarity, a method of similarity indices proposed by Richards *et al.*[12–14] was applied to study the electrostatic and shape similarity of two molecules. The electrostatic-similarity index (R_{AB})[13] is defined by eqn (1), where ε_A and ε_B are electrostatic potentials of molecules A and B, respectively, at a point outside the two molecules superimposed. The value of the index varies in the range of -1 to $+1$, with $R_{AB} = 1$ indicating perfect similarity. The shape-similarity index (S_{AB})[14] is defined in same manner by eqn (2), where T_A and T_B are the volumes of the individual molecules A and B, respectively, and C is the volume commonly shared by the two molecules at the superimposition.

$$R_{AB} = \int \varepsilon_A \varepsilon_B \, d\tau \Big/ \left(\int \varepsilon_A^2 \, d\tau \int \varepsilon_B^2 \, d\tau \right)^{1/2} \qquad (-1 \leqq R_{AB} \leqq 1) \qquad (1)$$

$$S_{AB} = C/(T_A T_B)^{1/2} \qquad (0 \leqq S_{AB} \leqq 1) \qquad (2)$$

In the calculation of the similarity index, R_{AB}, the values of ε_A and ε_B were calculated at each grid point of 0·5 Å intervals within the distance of 3·0 Å from the edge of the van der Waals surfaces of each molecule, and the space within the van der Waals surfaces of the two molecules was excluded from the calculation. In this study, the optimum superimposition of two molecules to maximize the shape-similarity index (S_{AB}) was obtained by simplex optimization procedure,[15] then the electrostatic similarity (R_{AB}) was computed at the superimposition. The calculations of similarity indices and simplex optimization were performed on SGI IRIS-4D workstation.

3 RESULTS AND DISCUSSION

3.1 Similarity–activity correlation in the amine moiety

A series of compounds having various structures in the amine moiety (Fig. 2) were studied to examine the correlation between molecular similarity and activity for cyclic and acyclic amine structures in neonicotinoids. The 6-chloro-3-pyridylmethyl group in these compounds was replaced by methyl to simplify the model, and the geometry and ESP atomic charges of the model molecules were obtained by MNDO-PM3. Among this series of compounds, the most active (**1**) having a nitro-

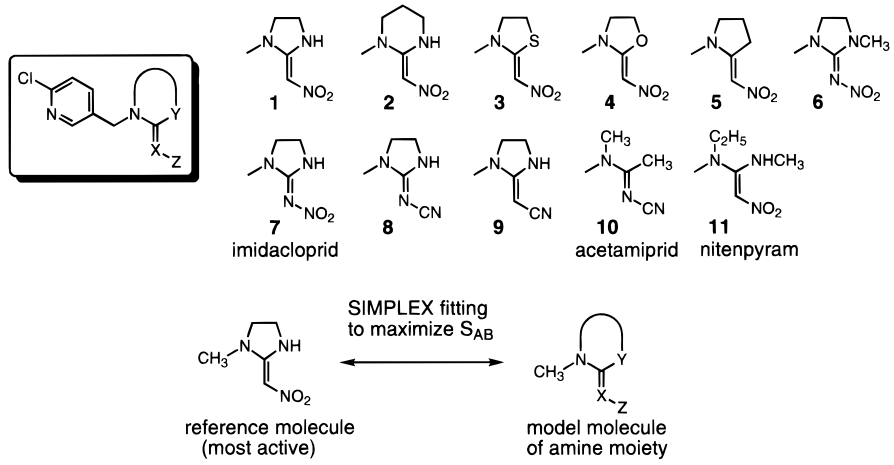


Fig. 2. Structural variation in the amine moiety and superimposition of model molecules by simplex procedure. The 6-chloro-3-pyridylmethyl group is replaced by methyl in the model molecules used in the calculations.

ethene structure was chosen as the reference. The model molecules of other compounds were superimposed onto the model of **1** by simplex optimization procedure to maximize the shape-similarity index (S_{AB}), then the electrostatic similarity (R_{AB}) was computed at the optimum superimposition (Fig. 2, Table 1).

The receptor-binding activity (pK_i) and the similarity index (R_{AB}) of compounds with cyclic amine structures (**1**–**9**) were plotted in Fig. 3, showing excellent correlation ($r = 0{\cdot}940$). Addition of acetamiprid (**10**), which has no cyclic amine structure, also gave significant correlation ($r = 0{\cdot}915$). However, another acyclic amine derivative, nitenpyram (**11**), was out of the correlation. Although the reason for the outlying plot for **11** is not clear, we speculate that the contribution of tautomeric structural change in **11** may be a possible reason. According to our NMR studies of a nitenpyram analog, a tautomeric form having an imine structure was observed in aqueous solution especially in acidic conditions (Fig. 4) (Kawai, T. *et al.*, unpublished). However, the tautomeric structural change in the reference compound **1** and an *N*-nitroguanidine derivative was not

TABLE 1
Receptor-Binding Activity (pK_i), Similarity Indices (S_{AB} and R_{AB}), and Atomic Charge at Amino Nitrogen of Compounds Having Various Structures in the Amine Moiety

		Similarity indices[b]		*Atomic charge*[c]	
Compound	pK_i [a]	S_{AB} [d]	R_{AB} [e]	*Mulliken*[f]	*ESP*[g]
1	7·68	1·000	1·000	0·0038	−0·3103
2	7·55	0·901	0·976	0·0365	−0·3273
3	6·94	0·929	0·971	0·0102	−0·0714
4	6·51	0·941	0·957	−0·0149	−0·3081
5	6·44	0·962	0·983	0·0325	−0·2626
6	3·79	0·855	0·848	0·0332	−0·2180
7	5·81	0·948	0·916	0·0353	−0·2640
8	5·16	0·913	0·919	0·0163	−0·2474
9	4·75	0·919	0·917	0·0018	−0·3158
10	5·16	0·818	0·869	−0·0873	−0·2771
11	4·32	0·794	0·967	−0·0274	−0·2458

[a] K_i values were taken from Ref. 1.
[b] Calculated for the model molecules shown in Fig. 2.
[c] At amino nitrogen calculated by MNDO-PM3.
[d] Optimized by simplex procedure.
[e] Calculated for the optimum superimposition to maximize S_{AB}.
[f] Mulliken atomic charge.
[g] Electrostatic potential derived charge.

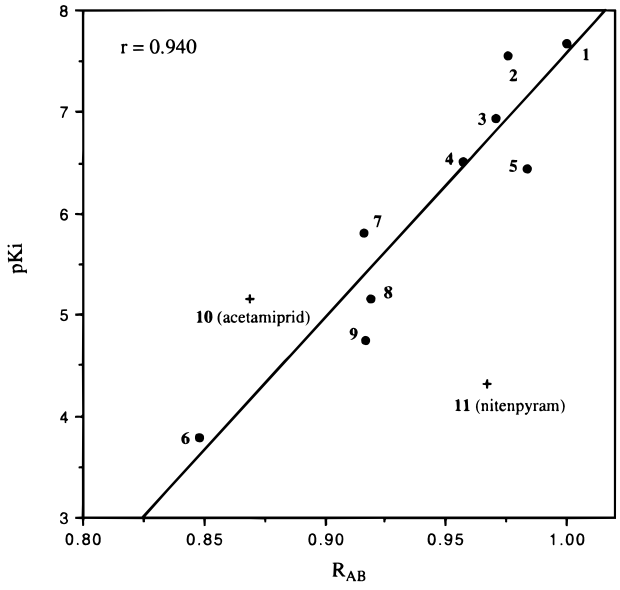


Fig. 3. Correlation between electrostatic similarity (R_{AB}) and receptor-binding activity (pK_i) for the amine moiety. The correlation coefficient ($r = 0{\cdot}940$) and the regression line were derived from the data excluding compounds **10** and **11**.

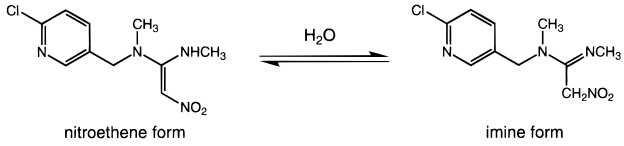


Fig. 4. Tautomeric structural change in a nitenpyram analog.

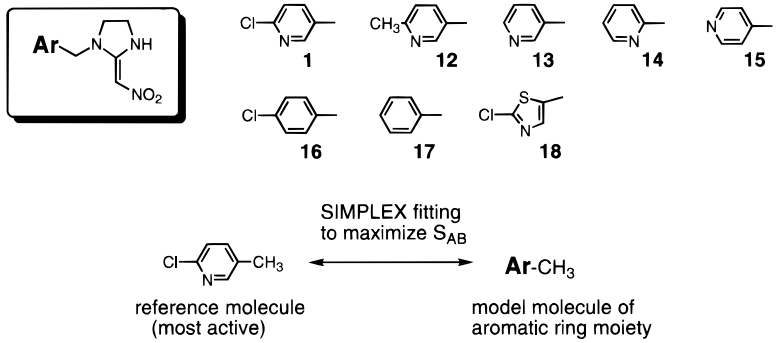


Fig. 5. Structural variation in the aromatic ring moiety and superimposition of model molecules by simplex procedure. The model molecules, Ar-CH_3, were used in the calculations.

TABLE 2
Receptor-Binding Activity (pK_i) and Similarity Indices (S_{AB} and R_{AB}) of Compounds Having Various Structures in the Aromatic Ring Moiety

		Similarity indices[b]	
Compound	pK_i [a]	S_{AB} [c]	R_{AB} [d]
1	7·68	1·000	1·000
12	6·33	0·976	0·976
13	7·08	0·915	0·988
14	4·92	0·886	0·286
15	3·87	0·882	0·545
16	5·93	0·971	0·652
17	5·61	0·896	0·567
18	7·09	0·906	0·939

[a] K_i values were taken from Ref. 1.
[b] Calculated for the model molecules shown in Fig. 5.
[c] Optimized by simplex procedure.
[d] Calculated for the optimum superimposition to maximize S_{AB}.

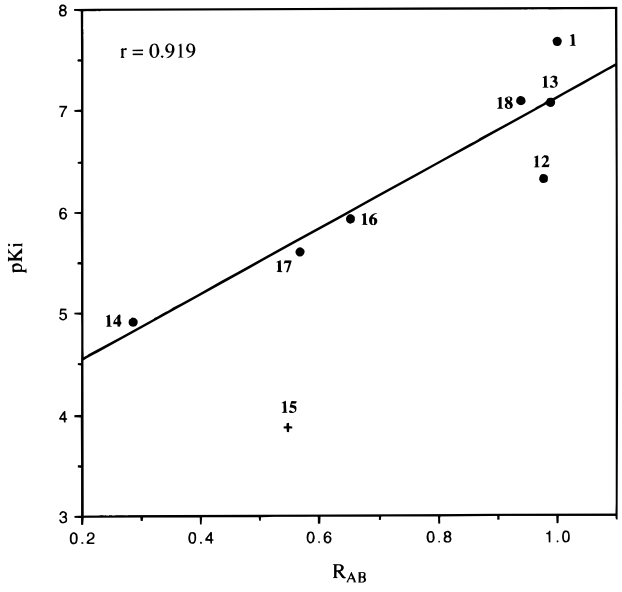


Fig. 6. Correlation between electrostatic similarity (R_{AB}) and receptor-binding activity (pK_i) for the aromatic ring moiety. The correlation coefficient ($r = 0·919$) and the regression line were derived from the data excluding compound **15**.

observed by NMR under similar conditions. The imine form of **11** is less similar to compound **1** ($R_{AB} = 0·647$) than the nitroethene structure, so that the receptor-binding activity of **11** may be reduced by taking such a tautomeric form in part.

3.2 Similarity–activity correlation in the aromatic ring moiety

A number of compounds having a variety of aromatic ring systems (Fig. 5) have been reported as neonicotinoids, among which the 6-chloro-3-pyridyl derivative (**1**) shows the most potent activity. Simplified model molecules of the aromatic ring moiety, Ar-CH_3, were subjected to the molecular similarity analysis, and the model of the most active compound (**1**) was chosen as the reference to which other molecules were superimposed to maximize the shape similarity (S_{AB}). The values of similarity indices (S_{AB} and R_{AB}) obtained for the optimum superimposition are shown in Table 2. A significant correlation between the activity (pK_i) and the electrostatic similarity (R_{AB}) was observed as shown in Fig. 6, in which the 4-pyridyl derivative was an unexpected outlier. Among the pyridyl derivatives, 3-pyridyl compounds (**1**, **12** and **13**) exhibited potent activity, whereas 2- and 4-pyridyl derivatives (**14** and **15**) were much less active. We speculate that the direction of elec-

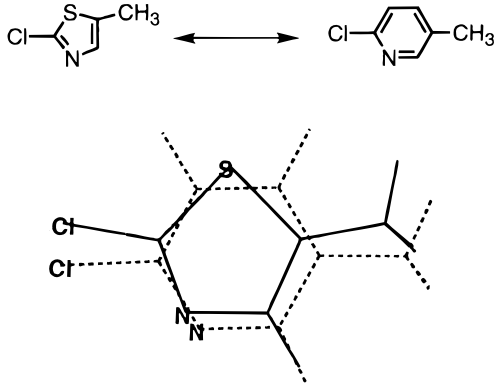


Fig. 7. Superimposition of the model molecules of 2-chloro-5-thiazolyl (solid lines) and 6-chloro-3-pyridyl (broken lines) derivatives to maximize the shape similarity index (S_{AB}).

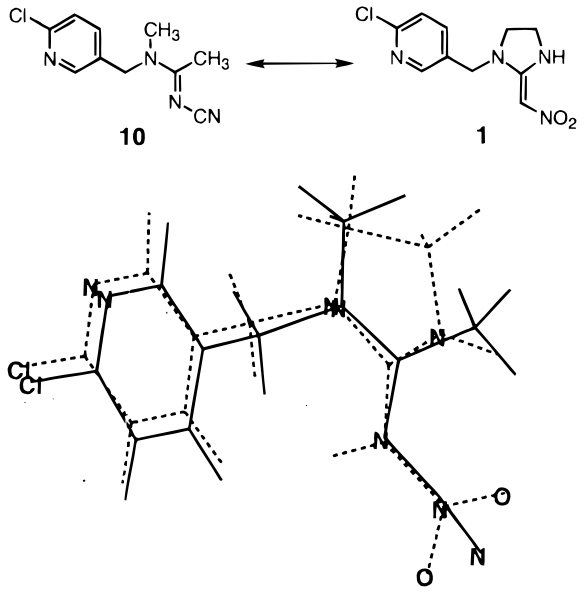


Fig. 8. Superimposition of acetamiprid (**10**) (solid lines) onto the reference molecule (**1**) (broken lines) to maximize the shape similarity index (S_{AB}).

trostatic or hydrogen-bonding interaction at the aromatic ring moiety may play an important role for the molecular recognition at the receptor. Such position-specific interactions at the pyridyl nitrogen may be predominant for the receptor binding. The similarity index, R_{AB}, which takes account of the distribution of electrostatic potentials around whole molecules, might not always be sufficient as a quantitative measure of the position-specific interaction.

2-Chloro-5-thiazolyl derivatives, such as compound **18**, have been known as active analogs of the 6-chloro-3-pyridyl derivative exhibiting potent activity. The

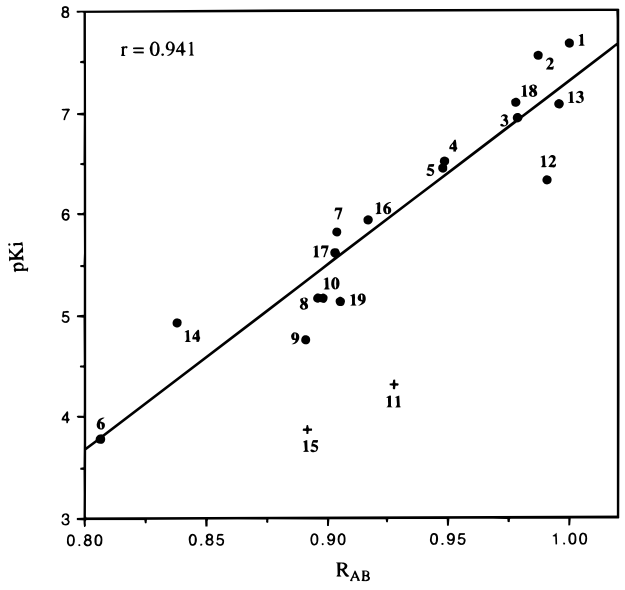
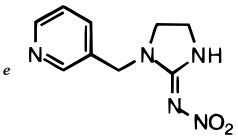


Fig. 9. Correlation between electrostatic similarity (R_{AB}) and receptor-binding activity (pK_i) for the whole molecule. The correlation coefficient ($r = 0{\cdot}941$) and the regression line were derived from the data excluding compounds **11** and **15**.

TABLE 3
Receptor-Binding Activity (pK_i) and Similarity Indices (S_{AB} and R_{AB}) of Compounds Having Various Structures both in the Amine and the Aromatic Ring Moieties

		Similarity indices[b]	
Compound	pK_i [a]	S_{AB} [c]	R_{AB} [d]
1	7·68	1·000	1·000
2	7·55	0·941	0·987
3	6·94	0·952	0·978
4	6·51	0·977	0·949
5	6·44	0·876	0·947
6	3·79	0·886	0·807
7	5·81	0·928	0·904
8	5·16	0·926	0·896
9	4·75	0·932	0·891
10	5·16	0·871	0·898
11	4·32	0·833	0·928
12	6·33	0·983	0·991
13	7·08	0·956	0·996
14	4·92	0·917	0·838
15	3·87	0·932	0·891
16	5·93	0·982	0·917
17	5·61	0·942	0·903
18	7·09	0·938	0·978
19[e]	5·14	0·893	0·905

[a] K_i values were taken from Ref. 1.
[b] Calculated for the whole molecules.
[c] Optimized by simplex procedure.
[d] Calculated for the optimum superimposition to maximize S_{AB}.
[e]



optimum superimposition of the model molecules of 2-chloro-5-thiazolyl and 6-chloro-3-pyridyl derivatives is shown in Fig. 7, through which the molecular similarity of these two molecules ($R_{AB} = 0{\cdot}939$, $S_{AB} = 0{\cdot}906$) may be understood.

3.3 Similarity–activity correlation in the whole molecule

The molecular similarity in the whole molecule was also studied for compounds with variation both in amine and aromatic ring moieties. Structures of each molecule were fully optimized by MNDO-PM3, and then superimposed onto the reference molecule (**1**) by simplex procedure to maximize the shape similarity (S_{AB}). The optimum superimposition of acetamiprid (**10**) onto the reference (**1**) is shown in Fig. 8 as an example. The electrostatic similarity (R_{AB}) obtained for the optimum superimposition and the receptor-binding activity (pK_i) are listed in Table 3, and plotted in Fig. 9. Equation (3) was obtained as a regression equation for the data in

Table 3, indicating the significant correlation between pK_i and R_{AB} computed for the whole molecules. In this equation, n represents the number of compounds, r the correlation coefficient, s the standard deviation and F the ratio of regression and residual variances. The figure in parentheses is the 95% confidence interval.

$$pK_i = 18{\cdot}16\ (\pm 3{\cdot}61)R_{AB} - 10{\cdot}87$$
$$n = 17,\ r = 0{\cdot}941,\ s = 0{\cdot}382,\ F_{1,15} = 115{\cdot}112 \quad (3)$$

The above equation was obtained for the data set excluding compounds **11** and **15** which were outlying from each regression line in the analyses for amine and aromatic ring moieties, respectively. The regression coefficient ($r = 0{\cdot}864$) for the data including **11** and **15** was considerably lower than in eqn (3). The plots for these two compounds in Fig. 9 deviate from the regression line as well as in Figs 3 and 6, reflecting specific structural features, such as tautomeric structural change and the position of pyridyl nitrogen.

3.4 Model of molecular recognition at nAChR

As a model of receptor-binding of neonicotinoids, Tomizawa and Yamamoto postulated that the amino nitrogen which is positively charged by an electron-withdrawing group plays the role of the cationic nitrogen in protonated nicotine at nAChR.[1] According to their hypothesis, we have examined the correlation between the atomic charge of the amino nitrogen and the receptor-binding activity. Mulliken atomic charge and ESP charge at the amino nitrogen in the model molecules of compounds **1**–**11** were obtained by MNDO-PM3 (Table 1). There was, however, no significant correlation between the atomic charges and activity. This suggests that the point charge on the nitrogen is not, on its own, sufficient to account for the receptor-binding activity.

On the other hand, the electrostatic similarity of molecules was significantly correlated with the receptor-binding activity, when each molecule was superimposed onto the most active one so as to maximize the molecular shape similarity. This indicates that the molecular similarity in terms of electrostatic properties is important for the activity as well as the superimposability in terms of molecular shape. The molecular electrostatic potentials of compound **1** are shown in Fig. 10, in which negative electrostatic potentials are distributed around the nitro group in the amine moiety and positive potentials are on the opposite side. The similarity in such a distribution of electrostatic potentials was quantitatively evaluated by the similarity index, and the index was found to correlate significantly with the receptor-binding activity. The negative potentials around the pyridyl nitrogen in the aromatic ring moiety are also characteristic, and the position-specific interaction between the pyridyl nitrogen and the receptor seems to play a significant role for the binding. We therefore propose an alternative model where the electrostatic

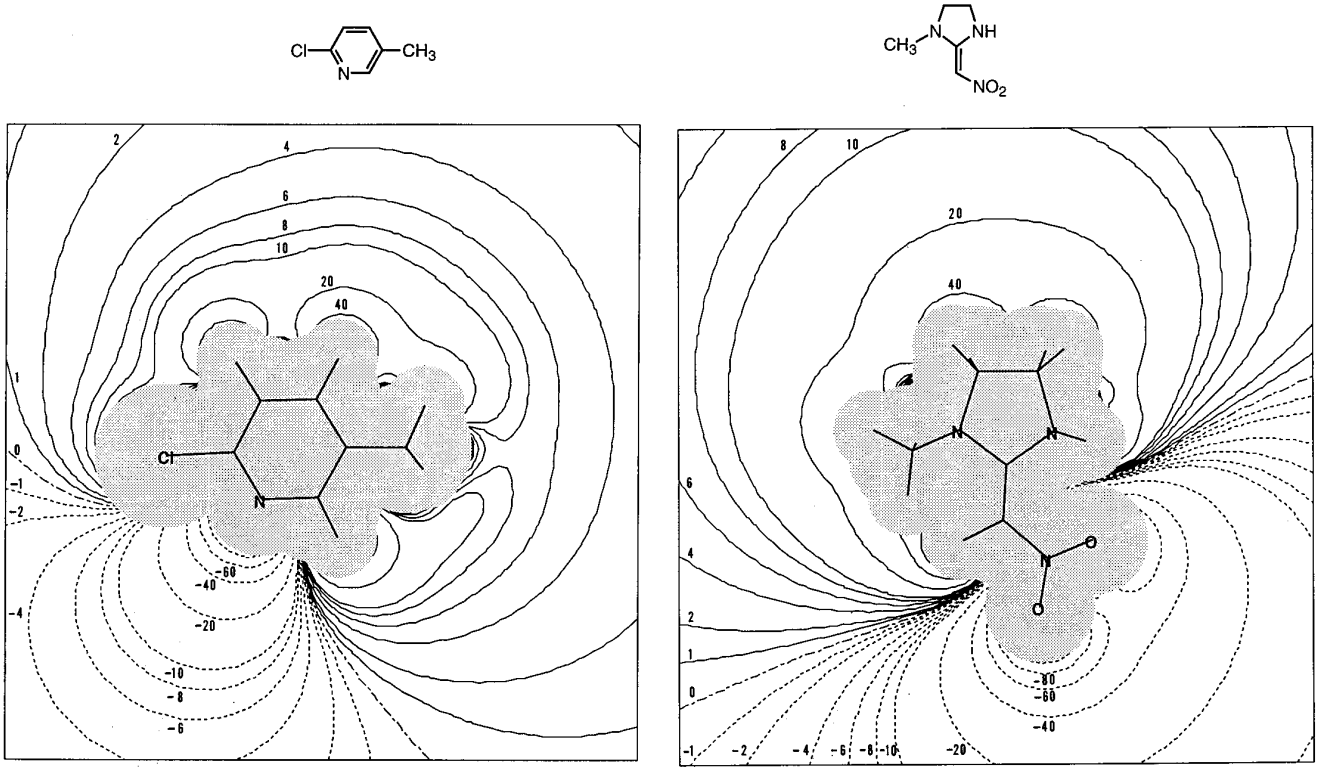


Fig. 10. Molecular electrostatic potentials of the cyclic amine moiety (right) and the pyridine ring (left) in compound **1**. Contour values are in unit of 10^{-3} au.

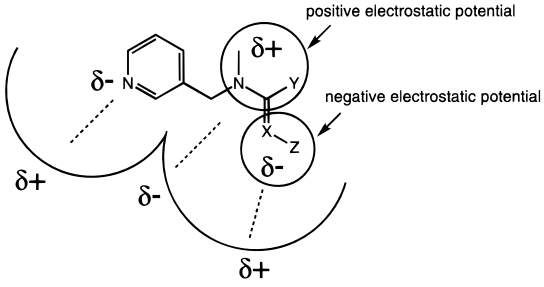


Fig. 11. A hypothetical model of molecular recognition of neonicotinoid insecticides at nAChR.

interaction is vital for molecular recognition at nAChR, as shown in Fig. 11.

As well as the electrostatic properties, the molecular shape similarity should be important for molecular recognition, since the optimum superimposition of molecules in terms of molecular shape gave a significant electrostatic parameter in the similarity-activity analysis.

4 CONCLUSION

As described above, the receptor-binding activity of various neonicotinoid insecticides was found to correlate quantitatively with the molecular similarity index. This indicates that the method of similarity index is helpful not only to understand the bioisosterism but also to provide useful descriptors in structure–activity analyses concerning molecular similarity. A schematic model of interaction between neonicotinoids and nAChR was drawn according to the result of similarity–activity analyses for a series of compounds shown in Fig. 1. Further studies including other nAChR agonists such as nicotine and its analogs are of interest, and biological and structural information of nAChR itself should also be expected to emerge to help further understanding of binding mechanism of the insecticides.

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